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Terms	Documents
liposome same (ph adj gradient) same mannitol	2

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DATE: Monday, December 12, 2005 Printable Copy Create Case

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L1: Entry 1 of 2 File: USPT Nov 16, 1993

DOCUMENT-IDENTIFIER: US 5262168 A
TITLE: Prostaglandin-lipid formulations

Brief Summary Text (17):
Thus, the present invention discloses a liposome composition which comprises an arachidonic acid metabolite which is preferably a prostaglandin, a lipid, a drying protectant, and a partition-enhancing buffer or buffering system. The prostaglandin is preferably prostaglandin E.sub.1. The liposomes can possess a transmembrane chemical potential such as a concentration gradient, which is preferably a pH gradient. The partition-enhancing buffer system comprises two solutions, one being a solution of a drying protectant, preferably a saccharide solution, and the second, preferably a citric acid solution. The saccharide solution is preferably dextrose, sucrose, or maltose, any of which may be combined with mannitol. Other protectants that may be used include dextran, poly (vinyl alcohol), or albumin. The pH of the protectant solution is preferably relatively basic, at about pH 3 to about pH 11, most preferably about pH 7. The drying protectant solution, preferably a saccharide solution, is present in about 5% to about 20% by weight, most preferably about 10% to about 12%. The liposome solution can then be size-reduced by, for example, an extrusion or homogenization procedure. The resulting solution can be dried by a dehydration or a lyophilization procedure. The citric acid solution is preferably of pH about 2.5 to about 4.5, more preferably pH 3.0.

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☐ 1. Document ID: US 5262168 A

Using default format because multiple data bases are involved.

L1: Entry 1 of 2 File: USPT Nov 16, 1993

US-PAT-NO: 5262168
DOCUMENT-IDENTIFIER: US 5262168 A

TITLE: Prostaglandin-lipid formulations

DATE-ISSUED: November 16, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lenk; Robert P.	Lambertville	NJ		
Tomsho; Michelle L.	Levittown	PA		
Suddith; Robert L.	Robbinsville	NJ		
Klimchak; Robert J.	Flemington	NJ		

US-CL-CURRENT: 424/450; 264/4.3, 264/4.6, 428/402.2, 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | [illegible] | Claims | KWIC | Draw D

☐ 2. Document ID: US 5082664 A

L1: Entry 2 of 2 File: USPT Jan 21, 1992

US-PAT-NO: 5082664
DOCUMENT-IDENTIFIER: US 5082664 A

TITLE: Prostaglandin-lipid formulations

DATE-ISSUED: January 21, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lenk; Robert P.	Lambertville	NJ		
Tomsho; Michelle L.	Levittown	PA		
Suddith; Robert L.	Robbinsville	NJ		
Klimchak; Robert J.	Flemington	NJ		

US-CL-CURRENT: 424/450; 264/4.3, 428/402.2, 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

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Terms	Documents
liposome same (ph adj gradient) same mannitol	2

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Refine Search

Search Results -

Terms	Documents
L1 and (ph adj gradient)	24

Database: US Pre-Grant Publication Full-Text Database; US Patents Full-Text Database; US OCR Full-Text Database; EPO Abstracts Database; JPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L2

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Search History

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DB=USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L2	L1 and (ph adj gradient)	24	L2
L1	liposome same kit	509	L1

END OF SEARCH HISTORY

5762957

L2: Entry 24 of 24 File: DWPI Jun 9, 1998

DERWENT-ACC-NO: 1998-347242
DERWENT-WEEK: 199830

TITLE: Kits for loading vesicles with chemical species, e.g. drug - use pH gradient imposed on vesicles to encapsulate species

Basic Abstract Text (1):
Kit for loading liposome vesicles, which have a membrane permeable to a chemical species (CS) to be loaded, comprises: (a) a first compartment including a first solution (S1) which comprises liposome vesicles; (b) a second compartment which has a second solution (S2); and (c) a charged CS which is present in either S1 or S2. The vesicles comprise: (i) an acid, which is impermeable through the vesicle, giving an acidic vesicle-containing aqueous medium in which the acid is present in the internal and external liposome phases; or (ii) a base, which is impermeable through the vesicle, giving a basic vesicle-containing aqueous medium in which the base is present in the internal and external liposome phases. S2 comprises: (i') a base which will induce a cationic CS to pass into the liposomes internal acidic aqueous phase; or (ii') an acid which will induce an anionic CS to pass into the liposomes internal basic aqueous phase. The CS is cationic when the first compartment comprises an acid, and is anionic when the first compartment comprises a base. Also claimed are: (A) a kit for loading liposome vesicles (which have a membrane permeable to an acidic or basic compound to be loaded), comprising: (a) a first compartment including a first solution (S1') which comprises liposome vesicles, which are as above; (b) a second compartment which includes a second solution (S2'); and (c) a third compartment including a compound which, when combined with S1', will produce a solution with a physiologically benign pH with regard to the blood of a mammal. S2' comprises a compound (or mixture of compounds) which, when combined with S1', will adjust the pH of S1' so as to provide a pH gradient between (i) S1' within the vesicle and (ii) S2'; and (B) a kit for loading liposome vesicles, which have a membrane permeable to a CS to be loaded, comprising: (a) a first compartment including a first solution (S1'') which has a selected pH and comprises liposome vesicles, where S1''; (i) has an internal liposome phase and an external liposome phase, (ii) is impermeable through the vesicle, and (iii) is present in the internal and external liposome phases; and (b) a second compartment including a second solution (S2'') which has a pH which is lower or higher than the selected pH of S1'', which will induce an ionic CS to pass into the liposomes' internal aqueous phase. The ionic CS is present in either S1'' or S2''. The CS is anionic when S2'' is more acidic than S1'', or is cationic when S2'' is more basic than S1''.

Basic Abstract Text (2):
USE - The kits may be used for accumulation of drugs (or other chemicals) within synthetic, lipid-like vesicles, using a pH gradient imposed on the vesicles just prior to use.

Standard Title Terms (1):
KIT LOAD VESICLE CHEMICAL SPECIES DRUG PH GRADIENT IMPOSE VESICLE ENCAPSULATE SPECIES

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L2: Entry 19 of 24 File: USPT Jun 9, 1998

DOCUMENT-IDENTIFIER: US 5762957 A
TITLE: Method for loading lipid like vesicles with drugs of other chemicals

Abstract Text (1):
A method for accumulating drugs or other chemicals within synthetic, lipid-like vesicles by means of a pH gradient imposed on the vesicles just prior to use is described. The method is suited for accumulating molecules with basic or acid moieties which are permeable to the vesicles membranes in their uncharged form and for molecules that contain charge moieties that are hydrophobic ions and can therefore cross the vesicle membranes in their charged form. The method is advantageous over prior art methods for encapsulating biologically active materials within vesicles in that is achieves very high degrees of loading with simple procedures that are economical and require little technical expertise, furthermore kits which can be stored for prolonged periods prior to use without impairment of the capacity to achieve drug accumulation are described. A related application of the method consists of using this technology to detoxify animals that have been exposed to poisons with basic, weak acid or hydrophobic charge groups within their molecular structures.

Brief Summary Text (2):
The invention relates to a method for loading liquid-like vesicles with a drug or other chemical species by establishing a preimposed pH gradient.

Brief Summary Text (10):
In accordance with an embodiment of the present invention, a method is set out for loading lipid-like vesicles having a membrane permeable to a chemical species to be loaded from a loading solution wherein the concentration of the loaded chemical species within the vesicle is greater than the concentration of the chemical species in the loading solution and the loaded chemical species can be substantially maintained within the vesicle for at least one-quarter hour following loading. The method comprises inducing a pH gradient across the vesicle membrane while the vesicle is in the loading solution containing the chemical species with the pH gradient having been selected to drive the chemical species into the vesicles.

Brief Summary Text (11):
In accordance with a second aspect of the present invention, a method is set out for loading lipid-like vesicles having a membrane permeable to a chemical species to be loaded and having the capability to maintain the loaded chemical species within the vesicle for at least one-quarter hour following loading by inducing a pH gradient across the membrane. The method comprises incorporating within the vesicle a buffer solution buffered to a selected acid or alkaline pH and having a selected molarity and at least one selected pKa approximately equal to the selected buffer pH. The membrane is substantially impermeable to the buffer for at least one-quarter hour following loading of the chemical species and the vesicles are positioned in a bulk solution having a selected pH. The term "solution" is sometimes used loosely in the application to indicate a suspension in instances where lipid-like vesicles are present (i.e. suspended) in a solution.

Brief Summary Text (17):

The kit further comprises a second separate compartment having a first substance (a compound or a second solution etc.) which when combined with the first solution will adjust the pH of the first solution so as to provide a predetermined pH gradient between the buffer within the vesicle and the pH adjusted first solution what will drive the chemical species into the vesicles. The kit also includes a third separate compartment having a second substance (yet another compound or a third solution etc.) which when combined with the pH adjusted first solution will further change the pH of said pH adjusted first solution to a value physiologically benign with regard to the blood of a mammal.

Brief Summary Text (19):
In accordance with a still further aspect of the present invention, a method is set forth for loading lipid-like vesicles having a membrane permeable to a chemical species to be loaded and the substantially maintaining the loaded chemical species within the vesicle for at least one-quarter hour following loading by inducing a pH gradient across the membrane. The method comprises incorporating within the vesicle a buffer solution buffered to a selected acid or alkaline pH and having a selected molarity at least one selected pKa approximately equal to the selected pH. The membrane is substantially impermeable to the buffer for at least one-quarter hour following loading. The vesicles are positioned in a bulk solution having a selected pH of either 0.5 to 3 pH units lower or higher than the pH of the buffer thereby establishing a transmembrane electrical potential. The inside of the vesicle will be positively charged if the pH outside the vesicle is more acid than inside or the inside of the vesicle will be negatively charged if the pH outside the vesicle is more basic than inside. The bulk solution is provided with a chemical species having membrane-permeable negatively charged ions if the membrane charge within the vesicle is positive or membrane-permeable positively charged ions if the membrane charge within the vesicle is negative.

Detailed Description Text (2):
In accordance with aspects of the present invention, a method and kits are provided for quickly and efficiently loading vesicles have a membrane permeable to a chemical species having one or more selected acid pH responsive groups or basic pH responsive groups by inducing a pH gradient across the membrane of the vesicle. The vesicles contain a buffer solution buffered to a selected acid pH if the pH responsive groups of the chemical species are basic or an basic pH if the pH responsive groups of the chemical species or drug are acid.

Detailed Description Text (3):
The movement of many molecules across a vesicle membrane involves proton gradients (pH gradients) as the driving force (Rottenberg, H., "The Measurement of Membrane Potential and .DELTA.pH in Cells Organelles, and Vesicles", Meth. Enzymol, 55:547-569 (1979), Reinhold, L. and A. Kaplan, "Membrane Transport of Sugars and Amino Acids", Ann. Rev. Plant Physiol., 35:45-83 (1984). Electron spin residence (ESR) methods have been used to measure transmembrane pH gradients. Spin-labelled amines and carboxylic acids (amines and acids labelled with nitroxide free radicals) such as Tempamine and Tempacid have been used as probes to measure the pH gradient. These probes are freely permeable to the membranes and the relative concentration of the probes within the vesicles provided a direct measurement of the pH gradient. ESR spectroscopy monitors probe partitioning between the aqueous and membrane phases giving easily resolvable signals. The effectiveness of the spin labelled nitroxide probes for determining transmembrane pH gradients has been well documented in both bacterial and animal systems. (Mehlhorn, R. and I. Probst, Meth. Enzymol., 88:334-344 (1982) and Melandri, B., R. Mehlhorn, and L. Packer, "Light-Induce Proton Gradients and Internal Volumes and Chromaphores of Rhodopseudomonas Spheaeroides", Arch. Biochem. Biophys., 235:97-105 (1984). However, in these previous studies these pH responsive molecules (spin labeled amines and weak acids) were used only as probes. Since these studies involved the determination of transmembrane pH gradients only very low concentrations of the pH-responsive molecules could be used so as to avoid disturbing the pH gradient being studied

which was generated as a result of natural processes, e.g., the so-called proton-motive force in mitochondrial respiration.

Detailed Description Text (6):
The method and the kits utilize a preimposed pH gradient between the buffer in the vesicles and the solution containing the vesicles to cause the desired chemical or drug to be accumulated and encapsulated by the vesicles. The general rule is that for every unit of pH difference a tenfold accumulation of the chemical occurs. For drugs containing several titratable groups the accumulation behavior is altered. Thus a drug which has two amino groups, having pKa's that are greater than the pH of the final solution, can be accumulated a hundred-fold with a pH gradient of one unit. A drug with three such amino groups can be accumulated a thousand-fold in the presence of a one-unit pH gradient etc. Conversely for a multi-acid drug, its pKa must be less than the pH of the final solution, for such substantial accumulation to occur.

Detailed Description Text (7):
The chemicals or drugs that may be incorporated using the present method of encapsulation include those species that have acid or basic pH responsive groups, hydrophobic delocalized charged ions or that may be provided with such. The vesicle is prepared by the entrapment of a buffer which will not permeate the membrane in the preparation of the vesicle. The buffer is selected so as to establish the pH gradient required to take up the specific chemical species or drug. The preparation of the vesicle is carried out by stirring and sonication. If the vesicles are to be administered, parenterally, in the solution that provides the external portion of the pH gradient, they are prepared in a buffer that is either more acidic or more alkaline than the physiological pH that they will encounter in the animal.

Detailed Description Text (8):
Subsequently the vesicles are treated with an alkaline or acid buffer, respectively, which will not permeate the vesicles membrane, thereby causing a pH change on the exterior but not interior of the vesicles. The resulting vesicles will therefore have a pH gradient between their interior and exterior. This gradient provides the driving force for accumulating the drug or chemical within the vesicle interior. As stated before, the larger the pH gradient, the larger the concentration gradient of the drug or chemical. Although a gradient of any magnitude will accumulate a drug, considerations of directing the drug to specific tissues, while minimizing its effects on non-targeted tissues dictate that the pH gradients be maximized.

Detailed Description Text (9):
The practical limits of the pH gradients are set by the tolerance of lipid-like material that is used in preparing the vesicles. For simple biological lipids like soybean phosphatides pH extremes of 4 and about 10.5 are readily tolerated for extended periods of time. The actual pH limits for a particular preparation of vesicles could be significantly larger, depending on how long the vesicles are to be stored which in turn depends on the stability of their lipid-like constituents. For example, vesicles to be loaded with amines are prepared in the presence of an acidic buffer such as citrate that has a pKa in the range of interest (usually about 5) and a pH of 4. This treatment ensures that the buffer will be contained within the liposome. Similarly, in cases where the liposomes are to be loaded with acidic molecules (carboxyl groups), the liposomes are prepared by sonication in the presence of a impermeable alkaline buffer that has a pKa of about 10.

Detailed Description Text (11):
After the vesicle has been prepared, the pH of the solution containing the vesicle is usually adjusted by the addition of an acid or a base to a pH of, respectively, at least about 0.5, 0.3 or 0.2 pH units higher than the pH of the buffer if the buffer is acidic and the chemical species has respectively one, two or three or more basic pH responsive groups and at least about 0.5, 0.3 or 0.2 pH units lower

than the pH of the buffer if the buffer is basic and the chemical species has respectively one, two or three or more acid pH responsive groups. In instances where it is desirable to inject the animal immediately with the vesicle containing solution having the adjusted pH, the pH is adjusted to a physiologically benign value of between about 7 and about 7.8, preferably about 7.4. This adjustment of the pH by addition of an acid or base establishes a pH gradient that drives the weak acid or base (i.e., the chemical species), into the vesicle interior. The chemical's loading rate will depend on the pKa and will be complete within less than a minute for low molecular weight (MW less than 500) amine chemicals with pKas less than 10 and having no charge or strongly polar groups other than the amino group. Analogously, weak acids having pKas greater than 4 will accumulate in the liposomes in about one minute, unless they bear strongly polar groups other than their carboxyls. For simple amine chemicals having a pKa greater than 11 equilibration will be slower than one minute. Analogously, a simple weak acid having a pKa lower than 4 will require more than one minute for equilibration. For more polar compounds, equilibration rates have to be determined for the specific chemicals.

Detailed Description Text (14):
After incorporation the chemical will remain in the vesicle for fifteen minutes to several hours depending on the chemicals, until the buffer leaks out of the vesicle. One should be aware that decay of the initial drug content may occur because of dilution of the water volume outside of the vesicles when they are injected into an animal. This decay will generally occur much more slowly than the initial loading process because of favorable effects of the pH gradient on the vectorial movement of the drug across the vesicle membrane. This insures that a drug will reach its targeted tissue before significant leakage out of the vesicles can occur. This time period of usually several hours allows the chemical or drug to be carried to its desired destination and prevents it from acting in areas that would be deleterious to the animal.

Detailed Description Text (15):
This technique of incorporating a chemical species within a lipid-like vesicle containing a preselected buffer by means of a pH gradient can be used to rescue clinical patients who have received toxic overdoses of drugs having acid or basic pH responsive groups (amine or carboxyl functions, etc.). Such drugs include a host of molecules such as general anesthestics, barbiturates (weak acids), aspirin, and other salicylates (acids) for which antidotes are not available. Injections of large volumes of the lipsomes suspended in a solution having a physiologically benign pH (usually about 7.4) can divert the drugs from their normal biological targets such as nerve cells to the liver where they will be metabolized and henced detoxified. For some drugs like aspirin, where elimation from the body does not involve significant liver metabolism, liposome injection would nevertheless provide a means for diminishing the toxic effect of the drug by reducing high blood concentration during the initial phase of intoxication. The liposomes containing the toxin may also be removed by means of dialysis.

Detailed Description Text (16):
The kits, as described above, also utilizes a pH gradient to load lipid-like vesicles. Referring now to FIG. 1, it will be noted that the kit apparatus illustrated comprises a syringe (10) having a glass, plastic, etc. barrel (9) having a first compartment (12), having a first solution (13) and a second compartment (14) having a second solution (15). The first compartment (12) is separated from the second compartment (14) by an impermeable barrier (16) made of rubber, plastic or the like. The syringe (10) also comprises a plunger (18) and a needle (20). The needle is surrounded by a protective sheath (21). The first solution (13) contains the membranous vesicles (22) magnified in size in FIG. 1 so as to be visible, containing a buffer (24) having either an acid or alkaline pH. In most instances the buffer (24) and the first solution (13) will be identical with the vesicles (22) having been prepared in the first solution (13).

Detailed Description Text (20):
Liposomes of soybean lipids were prepared according to a variation of Miyamoto and Stoeckenius, supra by sonication of 1 gm of asolectin in the presence of 10 mls of 100 mM sodium citrate at pH 5.0. Spin-labeled primary amine Tempamine (Aldrich Chemical Co.) was added to 50 .mu.M citrate solution containing the pre-sonicated vesicles to give a final concentration of 20 .mu.M, and a sufficient amount of 5 molar sodium hydroxide was also added to the solution to raise the pH of the solution to 7.4. This resulted in a 300-fold accumulation of the Tempamine inside the vesicles within one minute of the addition of the base. The rate of uptake of the amine depends on the pKa of the amine. As determined by ESR spectroscopy the resulting pH gradient was stable for several hours.

Detailed Description Text (24):
Lipid vesicles, containing 15 mg/ml of Sigma Type II-S phosphatidyl choline were prepared by sonication in a 120 mM lysine/phosphate buffer (chloride-free) at pH 10.5. The total sonication time was three minutes, with intermittent cooling. The vesicles were incubated for two minutes with 20 .mu.M of the spin-labeled carboxylic acid, prepared by reacting 1M succinic anhydride with one equivalent of Tempamine in chloroform, in the presence of a sufficient amount of a 100 mM citric acid to lower the external pH to 6 (approximately 1 volume equivalent). Analysis of the intravesicular concentration of the spin-labeled acid by ESR spectroscopy revealed that a more than 1,000-fold increase had occurred in response to the imposed pH gradient.

Detailed Description Text (25):
The vesicles were then transferred into a piece of dialysis tubing that had been spread into a flattened geometry to minimize the diffusion path of internal molecules to its surface. When the dialysis tubing was placed in a large volume of phosphate buffer in isotonic saline solution, this system simulated the physiological situation that would arise when vesicles are injected into the blood, where dilution of the drug outside the vesicles would occur as the vesicles moved through the circulation. When the tubing was placed into a beaker containing more than a ten-fold excess of lysine buffer; the pH gradient that had been preimposed was largely collapsed upon mixing of the aqueous phases inside and outside of the tubing. Table I shows the kinetics of efflux of the spin-labeled acid out of the dialysis tubing, and also shows the kinetics of the same probe when incubated with vesicles that have not been subjected to a pH gradient.

Detailed Description Text (26):
It is clear from the data in Table I that when the intradialysis concentration of probes was examined at the end of the incubation period, the vesicles that had been loaded with the pH gradient had retained a much higher concentration of the acid than those without a pH gradient. This example also indicates that it is unnecessary to maintain the pH gradient subsequent to the chemical loading procedure.

Detailed Description Text (30):
Liposomes are prepared according to Example 1 or 2 and are concentrated by means of a standard filtration concentration to a concentration of approximately 50 mg asolectin per 1 ml of 100 mM sodium citrate. The resulting lipid-like solution is injected in mice as described in Example 2 such that the final infusion is approximately 1% of total fluid body volume of asolectin. This example indicates that large volumes of liposomes having substantial pH gradients can be injected into animals without serious adverse effects.

Detailed Description Text (33):
Vesicles are prepared at pH 4.5 as before. The vesicle solution contains 10 .mu.M of the cyanine dye dithiazanine iodide. To achieve internalization of the cyanine dye, the vesicles are mixed with a 100 mM solution of sodium triphosphate of

sufficient volume to raise the pH of the mixture to 7.4. This generates a pH gradient acid-inside in the vesicles and this pH gradient in turn generates an electrical gradient of about 180 millivolts, negative inside the vesicles. The positively charged cyanine dye, whose delocalized charge renders it membrane permeable, is driven into the vesicle interior in response to the electrical potential, reaching a final accumulation of a thousand fold relative to the aqueous solution outside of the vesicles. Since the vesicles are prepared with a internal volume of about 10%, the final cyanine concentration inside the vesicles is about 100 .mu.M, while the external cyanine concentration is about 100 nM.

Detailed Description Paragraph Table (1):
TABLE I _____ ESR signal leaking out of dialysis tubing containing vesicles that had been incubated with a spin labelled carboxylic acid in the presence and absence of a pH gradient. No pH gradient pH gradient Time (min) ESR signal Time (min) ESR signal _____ 3 0.09 15 0.11 10 0.15 30 0.12 20 0.17 45 0.15 40 0.18 internal 0.24 internal 3.0

_____

Other Reference Publication (5):
Deamer et al, "The Response of Fluorescent Amines to pH Gradients Across Liposomes Membranes", Biochemica et Biophysica Acta, 274:323-335 (1972).

Other Reference Publication (9):
Mehlhorn et al, "Light-induced pH Gradients Measured with Spin-Labeled Amine and Carboxylic Acid Probes: Application to Halobacterium halobiumCell Envelope Vesicles", 88:334-344 (1982).

Other Reference Publication (11):
Nichols et al, "Catecholamine Uptake and Concentration by Liposomes Maintaining pH Gradients", Biochemica et Biophysica Acta, 455:269-271 (1976).

CLAIMS:

1. A kit for loading liposome vesicles having a membrane permeable to a chemical species to be loaded comprising:

a first compartment including a first solution which comprises liposome vesicles, wherein said vesicles comprise:

(i) an acid which is substantially impermeable through the vesicle to give an acidic vesicle-containing aqueous medium in which the acid is present in the internal and external liposome phases; or

(ii) a base which is substantially impermeable through the vesicle to give a basic vesicle-containing aqueous medium in which the base is present in the internal and external liposome phases;

a second compartment having a second solution, wherein said second solution comprises

(i) a base which will induce a cationic chemical species to pass into the liposomes' internal acidic aqueous phase or

(ii) an acid which will induce an anionic chemical species to pass into the liposomes' internal basic aqueous phase; and

a charged chemical species which is present in either the first or the second solution, wherein said chemical species is cationic when said first compartment comprises an acid, and is anionic when said first compartment comprises a base.

8. A kit for loading liposome vesicles having a membrane permeable to an acid or basic compound to be loaded comprising:

a first compartment including a first solution which comprises liposome vesicles, wherein said vesicles comprise:

(i) an acid which is substantially impermeable through the vesicle to give an acidic vesicle-containing aqueous medium in which the acid is present in the internal and external liposome phases; or

(ii) a base which is substantially impermeable through the vesicle to give a basic vesicle-containing aqueous medium in which the base is present in the internal and external liposome phases;

a second compartment including a second solution, wherein said second solution comprises a compound or mixture thereof which when combined with the first solution will adjust the pH of the first solution so as to provide a pH gradient between the first solution within the vesicle and the second solution; and

a third compartment including a compound which when combined with the first solution will produce a solution having a physiologically benign pH value with regard to the blood of a mammal.

15. A kit for loading liposome vesicles having a membrane permeable to a chemical species to be loaded comprising:

a first compartment including a first solution having a selected pH which comprises liposome vesicles, wherein said solution (i) has an internal liposome phase and an external liposome phase; (ii) is substantially impermeable through the vesicle; and (iii) is present in the internal and external liposome phases;

a second compartment including (i) a second solution having a pH which is lower (more acidic) or higher (more basic) than the selected pH of the first solution which will induce an ionic chemical species to pass into the liposomes' internal aqueous phase; and

wherein said ionic chemical species is present in either the first or the second solution, and said species (i) is anionic when said second solution is more acidic than the first solution or (ii) is cationic when said second solution is more basic than the first solution.

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L2: Entry 17 of 24 File: USPT Jul 28, 1998

DOCUMENT-IDENTIFIER: US 5785987 A
TITLE: Method for loading lipid vesicles

Abstract Text (1):
Methods for the preparation of stable liposome formulations of protonatable therapeutic agents. The methods involve loading a therapeutic agent into preformed liposomes having a methylamine concentration gradient across the lipid bilayer of the liposomes. These methods provide liposome formulations which are more stable, more cost effective, and easier to prepare in a clinical environment than those previously available. The present invention also provides the pharmaceutical compositions prepared by the above methods, a kit for the preparation of liposome formulations of therapeutic agents, and methods for their use.

Brief Summary Text (8):
For drug encapsulation, there is a need to increase the trapping efficiency such that the drug to lipid ratio is as high as possible, while maintaining the original chemical integrity of both drug and lipid. Consequently, the drug loading process should be mild and not subject the lipids, liposomes or drugs to harsh conditions such as extreme pH, high temperatures, or both. Once administration to a patient has occurred, drug release is a factor. Rapid release of pharmaceuticals from liposomes reduces the biodistribution benefits sought in utilizing lipid vesicle carriers. Accordingly, efforts to optimize pharmaceutical loading and to reduce the rate of release of pharmaceuticals from lipid vesicles have continued. For clinical applications, the liposome formulations should also be capable of existing stably in a formulated state or in a ready-to-mix kit to allow for shipping and storage.

Brief Summary Text (11):
The present invention provides methods for the preparation of stable liposome formulations of protonatable therapeutic agents. The method involves loading a therapeutic agent into preformed liposomes having a methylamine concentration gradient across the lipid bilayer of the liposomes. This method provides liposome formulations which are more stable, more cost effective, and easier to prepare in a clinical environment than those previously available. Additionally, these methods have application to a broader spectrum of pharmaceutical agents than methods previously described. The present invention also provides the pharmaceutical compositions prepared by the above method, a kit for the preparation of liposome formulations of therapeutic agents, and methods for their use.

Detailed Description Text (41):
Despite this more "active" loading process, some of these methods still suffer from inefficient drug loading or limitations resulting from the particular media used. For example, Mayer, et al., J. Biol. Chem. 260:802-808 (1985), describe the loading of a local anesthetic dicubaine, into liposomes using Na+ and K+ gradients. However, only 52% loading was achieved. Methods which involve H+ ion gradients (or pH gradients) have proven useful for a number of liposome loading applications. Nevertheless, these methods also have their limitations. For example, one method which uses a pH gradient involves preparing liposomes having an acidic interior medium and a neutral exterior medium. The use of an unphysiologically acidic pH can degrade some drugs and also promote lipid hydrolysis and subsequent leakage of any encapsulated drug. Additionally, the method does not appear to be useful for those

drugs which have both a basic amine functionality and a carboxylic acid functionality (e.g., amino acids, small peptides and zwitterionic drugs). For example, Chakrabarti, et al. U.S. Pat. No. 5,380,531 describes pH loading methods for amino acids and peptides in which the amino acids and peptides are first derivatized to their ester or amide forms. Chakrabarti, et al. also note that the method does not work for the more basic amino acid esters and peptide esters such as histidine methyl ester, (Lys).sub.5 methyl ester and Lys-(Ala).sub.4 methyl ester. Other problems which exist for pH loading methods involve the limited solubility of some drugs in a neutral external medium. For example, the quinolone antibacterial agent ciprofloxacin is essentially insoluble in water in the pH range 6 to 8. If the external pH is lowered to about 5 (a point at which ciprofloxacin is adequately soluble) the gradient is insufficient for rapidly and efficiently loading the drug.

Detailed Description Text (47):
Liposomes which encapsulate an aqueous solution of a methylamine salt can be prepared by any of the methods described above. Subsequent loading of the protonatable therapeutic agent into the liposomes will be dependent on the methylamine concentration gradient (or methylammonium ion gradient) and the pH gradient which also results from a change in methylamine concentrations between the lipid bilayers. The gradients are created by forming liposomes in a methylammonium salt solution, followed by removal or dilution of the salt from the external aqueous phase of the liposomes. A number of methylammonium salts are useful in the present invention, including methylammonium chloride, methylammonium sulfate, methylammonium citrate and methylammonium acetate. Other salts which are suitable in pharmaceutical formulations are known to those of skill in the art. The concentration of the methylammonium salt solution which is encapsulated can vary from about 50 mM to about 1M, however concentrations of 200 mM to 800 mM are preferred, with 300 mM to 600 mM being particularly preferred. In general an initial methylammonium ion concentration of about 600 mM is the most preferred. To create the concentration gradient, the original external medium is replaced by a new external medium having a different concentration of the charged species or a totally different charged species. The replacement of the external medium can be accomplished by various techniques, such as, by passing the lipid vesicle preparation through a gel filtration column, e.g., a Sephadex column, which has been equilibrated with the new medium, or by centrifugation, dialysis, or related techniques.

Detailed Description Text (48):
Depending upon the permeability of the lipid vesicle membranes, the full transmembrane potential corresponding to the concentration gradient will either form spontaneously or a permeability enhancing agent, e.g., a proton ionophore may have to be added to the bathing medium. If desired, the permeability enhancing agent can be removed from the preparation after loading has been completed using chromatography or other techniques. In either case, a transmembrane potential having a magnitude defined by the Nernst equation will appear across the lipid vesicles' membranes. The change in composition of the external phase causes an outflow of neutral methylamine from the interior encapsulated medium to the external medium. This outflow also results in a reverse pH gradient by accumulation of hydrogen ions left behind in the internal aqueous phase. An influx of a neutral form of a protonatable therapeutic agent into the liposomes replaces the methylamine.

Detailed Description Text (65):
The present invention also provides liposomes and protonatable therapeutic agents in kit form. The kit will typically be comprised of a container which is compartmentalized for holding the various elements of the kit. The therapeutic agents which are used in the kit are those agents which have been described above. In one embodiment, one compartment will contain a second kit for loading a protonatable therapeutic agent into a liposome just prior to use. Thus, the first

compartment will contain a suitable agent in a neutral buffer which is used to provide an external medium for the liposomes, typically in dehydrated form in a first compartment. The liposomes are vesicles which have an encapsulated methylammonium salt. In other embodiments, the kit will contain the compositions of the present inventions, preferably in dehydrated form, with instructions for their rehydration and administration. In still other embodiments, the liposomes and/or compositions comprising liposomes will have a targeting moiety attached to the surface of the liposome. As noted in sections above, one striking advantage for the kits described is their broader applicability for the uptake and retention of drugs such as, for example, ciprofloxacin.

Detailed Description Text (75):
In the examples below, Example 1 illustrates difficulties associated with liposome uptake of ciprofloxacin using pH gradient methods. Example 2 illustrates differences in drug loading using a substituted ammonium ion gradient for the uptake of doxorubicin, vincristine and ciprofloxacin. Example 3 illustrates the use of a diamine for establishing ion gradients to facilitate drug uptake and the differences observed with different drugs. Example 4 illustrates the use of methylammonium sulfate to load a zwitterionic drug (ciprofloxacin) into liposomes. Example 5 illustrates attempts to load tryptophan (zwitterionic) into liposomes using methylammonium sulfate. Example 6 provides additional results for the loading of drugs into liposomes using methylammonium ion gradients and also shows the effect of vesicle composition, counterion, drug-to-lipid ratios and liposome surface conjugates. Examples 7 and 8 illustrate the retention of drugs in liposomes which were loaded using a methylammonium ion gradient.

Detailed Description Text (89):
This example illustrates the attempts to efficiently load liposomes with ciprofloxacin using a pH gradient.

Detailed Description Text (106):
This example illustrates the use of a methylammonium sulfate ion gradient to promote liposome uptake of ciprofloxacin and provides a comparison with the method above which utilizes EDAS or a pH gradient.

Detailed Description Text (111):
As noted above, ciprofloxacin is zwitterionic at neutral pH and exhibits characteristics which make active loading into liposomes by such processes as pH gradients, very difficult. Surprisingly, ciprofloxacin has been found to be loaded into liposomes using a methylamine/methylammonium ion gradient (see Example 4). To see if this behavior extends to other common zwitterionic compounds, the temperature-dependent uptake of the amino acid tryptophan was investigated. The results are provided in FIG. 9. The initial tryptophan/lipid ratio was 1.0 using 100 nm LUVs composed of DPPC/Chol (55:45). As can be seen in FIG. 9, essentially no uptake was observed at 45.degree. C. and very little (.about.5%) was observed at 60.degree. C. Thus, the ability to encapsulate ciprofloxacin does not extend to zwitterions such as tryptophan.

Detailed Description Text (129):
This example illustrates the reduction in the rate of release of charged drugs from lipid vesicles using methylamine and pH gradients.

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Search Results - Record(s) 1 through 24 of 24 returned.

☐ 1. Document ID: US 6831158 B2

Using default format because multiple data bases are involved.

L2: Entry 1 of 24 File: USPT Dec 14, 2004

US-PAT-NO: 6831158
DOCUMENT-IDENTIFIER: US 6831158 B2

TITLE: G-CSF conjugates

DATE-ISSUED: December 14, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nissen; Torben Lauesgaard	Palo Alto	CA		
Andersen; Kim Vilbour	Broenshoej			DK
Hansen; Christian Karsten	Vedbaek			DK
Mikkelsen; Jan Moller	Gentofte			DK
Schambye; Hans Thalsgaard	Frederiksberg			DK

US-CL-CURRENT: 530/397; 435/69.1, 435/69.4, 435/70.1, 435/71.1, 530/350, 530/351, 530/395, 530/399

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

☐ 2. Document ID: US 6794369 B2

L2: Entry 2 of 24 File: USPT Sep 21, 2004

US-PAT-NO: 6794369
DOCUMENT-IDENTIFIER: US 6794369 B2

TITLE: Methods, systems, and kits for intravascular nucleic acid delivery

DATE-ISSUED: September 21, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Newman; Christopher M. H.	Dore			GB
Brisken; Axel F.	Fremont	CA		

US-CL-CURRENT: 514/44; 435/455, 604/22, 604/28

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

☐ 3. Document ID: US 6773719 B2

L2: Entry 3 of 24 File: USPT Aug 10, 2004

US-PAT-NO: 6773719
DOCUMENT-IDENTIFIER: US 6773719 B2

TITLE: Liposomal compositions, and methods of using liposomal compositions to treat dislipidemias

DATE-ISSUED: August 10, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rodrigueza; Wendi V.	Ann Arbor	MI		
Williams; Kevin Jon	Wynnewood	PA		
Hope; Michael J.	Vancouver			CA

US-CL-CURRENT: 424/450; 428/402.2, 514/824

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

☐ 4. Document ID: US 6723338 B1

L2: Entry 4 of 24 File: USPT Apr 20, 2004

US-PAT-NO: 6723338
DOCUMENT-IDENTIFIER: US 6723338 B1
** See image for Certificate of Correction **

TITLE: Compositions and methods for treating lymphoma

DATE-ISSUED: April 20, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sarris; Andreas H.	Houston	TX		
Cabanillas; Fernando	Houston	TX		
Logan; Patricia M.	Vancouver			CA
Burge; Clive T. R.	Brentwood Bay			CA
Goldie; James H.	Vancouver			CA
Webb; Murray S.	Delta			CA

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

☐ 5. Document ID: US 6649358 B1

L2: Entry 5 of 24 File: USPT Nov 18, 2003

US-PAT-NO: 6649358
DOCUMENT-IDENTIFIER: US 6649358 B1

TITLE: Microscale assays and microfluidic devices for transporter, gradient induced, and binding activities

DATE-ISSUED: November 18, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Parce; J. Wallace	Palo Alto	CA		
Hodge; C. Nicholas	Los Altos Hills	CA		
Wada; H. Garrett	Atherton	CA		

US-CL-CURRENT: 435/7.2; 435/287.3, 435/288.5, 435/4, 435/7.1, 435/7.93, 436/538

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 6. Document ID: US 6646110 B2

L2: Entry 6 of 24 File: USPT Nov 11, 2003

US-PAT-NO: 6646110
DOCUMENT-IDENTIFIER: US 6646110 B2

TITLE: G-CSF polypeptides and conjugates

DATE-ISSUED: November 11, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nissen; Torben Lauesgaard	Frederiksberg			DK
Andersen; Kim Vilbour	Copenhagen			DK
Hansen; Christian Karsten	Vedbaek			DK
Mikkelsen; Jan Moller	Gentofte			DK
Schambye; Hans Thalsgard	Frederiksberg			DK

US-CL-CURRENT: 530/397; 435/2, 435/69.1, 435/69.4, 435/70.1, 435/71.1, 435/8, 514/12, 530/350, 530/351, 530/395, 530/399

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 7. Document ID: US 6555660 B2

L2: Entry 7 of 24 File: USPT Apr 29, 2003

US-PAT-NO: 6555660
DOCUMENT-IDENTIFIER: US 6555660 B2

TITLE: G-CSF conjugates

DATE-ISSUED: April 29, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nissen; Torben Lauesgaard	Frederiksberg			DK
Andersen; Kim Vilbour	Broenshoej			DK
Hansen; Christian Karsten	Vedbaek			DK
Mikkelsen; Jan Moller	Gentofte			DK
Schambye; Hans Thalsgaard	Frederiksberg			DK

US-CL-CURRENT: 530/397; 435/69.1, 435/69.4, 435/70.1, 435/71.1, 530/350, 530/351, 530/395, 530/399

Full | Title | Citation | Front | Review | Classification | Date | Reference | ... | Claims | KWIC | Draw D...

☐ 8. Document ID: US 6372498 B1

L2: Entry 8 of 24 File: USPT Apr 16, 2002

US-PAT-NO: 6372498
DOCUMENT-IDENTIFIER: US 6372498 B1

TITLE: Methods, systems, and kits for intravascular nucleic acid delivery

DATE-ISSUED: April 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Newman; Christopher M. H.	Sheffield			GB
Brisken; Axel F.	Fremont	CA		

US-CL-CURRENT: 435/455; 424/93.2, 424/93.21, 435/325, 514/44, 536/23.1, 604/19, 604/22, 604/28

Full | Title | Citation | Front | Review | Classification | Date | Reference | ... | Claims | KWIC | Draw D...

☐ 9. Document ID: US 6316024 B1

L2: Entry 9 of 24 File: USPT Nov 13, 2001

US-PAT-NO: 6316024
DOCUMENT-IDENTIFIER: US 6316024 B1

TITLE: Therapeutic liposome composition and method of preparation

DATE-ISSUED: November 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Allen; Theresa M.	Edmonton			CA
Uster; Paul	Tracy	CA		
Martin; Francis J.	San Francisco	CA		
Zalipsky; Samuel	Redwood City	CA		

US-CL-CURRENT: 424/450; 424/812, 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 10. Document ID: US 6056973 A

L2: Entry 10 of 24 File: USPT May 2, 2000

US-PAT-NO: 6056973
DOCUMENT-IDENTIFIER: US 6056973 A

TITLE: Therapeutic liposome composition and method of preparation

DATE-ISSUED: May 2, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Allen; Theresa M.	Edmonton			CA
Uster; Paul	Tracy	CA		
Martin; Francis J.	San Francisco	CA		
Zalipsky; Samuel	Redwood City	CA		

US-CL-CURRENT: 424/450; 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 11. Document ID: US 5939270 A

L2: Entry 11 of 24 File: USPT Aug 17, 1999

US-PAT-NO: 5939270
DOCUMENT-IDENTIFIER: US 5939270 A

TITLE: Markers for organ rejection

DATE-ISSUED: August 17, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Hauns.o slashed.; Stig	Rungsted	DK
Carlsen; J.o slashed.rn	Charlottenlund	DK
Kjeldsen; Keld	K.o slashed.benhavn .O slashed.	DK
Johansen; Thais Taaning	Skodsborg	DK
Larsen; Peter Mose	Aarhus C	DK
Jensen; Ulla Andrup	Galten	DK
Fey; Stephen John	Aarhus C	DK
Boutry; Marc	Brussels	BE
Degand; Herve	Havre-Mons	BE

US-CL-CURRENT: 435/7.1; 435/29, 435/4, 435/7.21, 435/7.92, 435/810, 435/975, 436/518, 436/536, 436/86, 530/350, 530/841

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 12. Document ID: US 5859219 A

L2: Entry 12 of 24 File: USPT Jan 12, 1999

US-PAT-NO: 5859219
DOCUMENT-IDENTIFIER: US 5859219 A

TITLE: Purified vacuolating toxin from Helicobacter pylori and methods to use same

DATE-ISSUED: January 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cover; Timothy L.	Nashville	TN		
Blaser; Martin J.	Nashville	TN		

US-CL-CURRENT: 536/22.1; 424/236.1, 435/252.3, 435/320.1, 435/69.1, 435/69.3, 435/91.1, 536/23.7, 536/24.3, 536/24.32

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 13. Document ID: US 5837282 A

L2: Entry 13 of 24 File: USPT Nov 17, 1998

US-PAT-NO: 5837282
DOCUMENT-IDENTIFIER: US 5837282 A

TITLE: Ionophore-mediated liposome loading

DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Fenske; David B.	Surrey	CA
Cullis; Pieter R.	Vancouver	CA
Wong; Kim	Vancouver	CA
Norbert; Maurer	Vancouver	CA
Leenhouts; Johanna M.	Vancouver	CA
Maurer; Elisabeth	Vancouver	CA
Boman; Nancy	Surrey	CA

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 14. Document ID: US 5820873 A

L2: Entry 14 of 24 File: USPT Oct 13, 1998

US-PAT-NO: 5820873
DOCUMENT-IDENTIFIER: US 5820873 A
** See image for Certificate of Correction **

TITLE: Polyethylene glycol modified ceramide lipids and liposome uses thereof

DATE-ISSUED: October 13, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Choi; Lewis S. L.	Burnaby			CA
Madden; Thomas D.	Vancouver			CA
Webb; Murray S.	Vancouver			CA

US-CL-CURRENT: 424/283.1; 424/1.21, 424/184.1, 424/450, 424/812, 436/529, 436/535, 514/885

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 15. Document ID: US 5814335 A

L2: Entry 15 of 24 File: USPT Sep 29, 1998

US-PAT-NO: 5814335
DOCUMENT-IDENTIFIER: US 5814335 A

TITLE: Sphingosomes for enhanced drug delivery

DATE-ISSUED: September 29, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Webb; Murray S.	Vancouver			CA

Bally; Marcel B.	Bowen Island	CA
Mayer; Lawrence D.	N. Vancouver	CA
Miller; James J.	Vancouver	CA
Tardi; Paul G.	Richmond	CA

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 16. Document ID: US 5800833 A

L2: Entry 16 of 24 File: USPT Sep 1, 1998

US-PAT-NO: 5800833
DOCUMENT-IDENTIFIER: US 5800833 A

TITLE: Method for loading lipid vesicles

DATE-ISSUED: September 1, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hope; Michael	Vancouver			CA
Cullis; Pieter R.	Vancouver			CA
Fenske; David	Surrey			CA
Wong; Kim	Vancouver			CA

US-CL-CURRENT: 426/450; 264/4.1, 264/4.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 17. Document ID: US 5785987 A

L2: Entry 17 of 24 File: USPT Jul 28, 1998

US-PAT-NO: 5785987
DOCUMENT-IDENTIFIER: US 5785987 A

TITLE: Method for loading lipid vesicles

DATE-ISSUED: July 28, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hope; Michael	Vancouver			CA
Cullis; Pieter R.	Vancouver			CA
Fenske; David B.	Surrey			CA
Wong; Kim F.	Vancouver			CA

US-CL-CURRENT: 424/450; 264/4.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 18. Document ID: US 5780054 A

L2: Entry 18 of 24 File: USPT Jul 14, 1998

US-PAT-NO: 5780054
DOCUMENT-IDENTIFIER: US 5780054 A

TITLE: Methods for increasing the circulation half-life of protein-based therapeutics

DATE-ISSUED: July 14, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tardi; Paul G.	Richmond			CA
Swartz; Erik	Vancouver			CA
Bally; Marcel B.	Bowen Island			CA
Cullis; Pieter R.	Vancouver			CA

US-CL-CURRENT: 424/450; 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 19. Document ID: US 5762957 A

L2: Entry 19 of 24 File: USPT Jun 9, 1998

US-PAT-NO: 5762957
DOCUMENT-IDENTIFIER: US 5762957 A

TITLE: Method for loading lipid like vesicles with drugs of other chemicals

DATE-ISSUED: June 9, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mehlhorn; Rolf Joachim	Richmond	CA		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 20. Document ID: US 5741516 A

L2: Entry 20 of 24 File: USPT Apr 21, 1998

US-PAT-NO: 5741516
DOCUMENT-IDENTIFIER: US 5741516 A

TITLE: Sphingosomes for enhanced drug delivery

DATE-ISSUED: April 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Webb; Murray S.	Vancouver			CA
Bally; Marcel B.	Bowen Island			CA
Mayer; Lawrence D.	N. Vancouver			CA
Miller; James J.	Vancouver			CA
Tardi; Paul G.	Richmond			CA

US-CL-CURRENT: 424/450; 514/27, 514/283

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 21. Document ID: US 5583052 A

L2: Entry 21 of 24 File: USPT Dec 10, 1996

US-PAT-NO: 5583052
DOCUMENT-IDENTIFIER: US 5583052 A

TITLE: Formulation preparation device

DATE-ISSUED: December 10, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Portnoff; Joel B.	Langhorne	PA		
Coe; Royden M.	Bordentown	NJ		
Grimm; John	Schnecksville	PA		
Raines; Kenneth	Bethlehem	PA		
Bartholomew; Joel	Danielsville	PA		

US-CL-CURRENT: 436/180; 422/103

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 22. Document ID: US 5543152 A

L2: Entry 22 of 24 File: USPT Aug 6, 1996

US-PAT-NO: 5543152
DOCUMENT-IDENTIFIER: US 5543152 A

TITLE: Sphingosomes for enhanced drug delivery

DATE-ISSUED: August 6, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Webb; Murray S.	Vancouver			CA
Bally; Marcel B.	Bowen Island			CA
Mayer; Lawrence D.	North Vancouver			CA

US-CL-CURRENT: 424/450; 514/27, 514/283

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 23. Document ID: US 5213804 A

L2: Entry 23 of 24 File: USPT May 25, 1993

US-PAT-NO: 5213804
DOCUMENT-IDENTIFIER: US 5213804 A
** See image for Certificate of Correction **

TITLE: Solid tumor treatment method and composition

DATE-ISSUED: May 25, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Martin; Francis J.	San Francisco	CA		
Woodle; Martin C.	Menlo Park	CA		
Redemann; Carl	Walnut Creek	CA		
Yau-Young; Annie	Palo Alto	CA		

US-CL-CURRENT: 424/450; 424/426, 424/78.31

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 24. Document ID: US 5762957 A

L2: Entry 24 of 24 File: DWPI Jun 9, 1998

DERWENT-ACC-NO: 1998-347242
DERWENT-WEEK: 199830
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TITLE: Kits for loading vesicles with chemical species, e.g. drug - use pH gradient imposed on vesicles to encapsulate species

INVENTOR: MEHLHORN, R J

PRIORITY-DATA: 1985US-0776826 (September 17, 1985), 1988US-0220388 (July 12, 1988), 1990US-0547382 (July 3, 1990), 1991US-0741305 (August 7, 1991), 1995US-0474382 (June 7, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5762957 A	June 9, 1998		011	A61K009/127

INT-CL (IPC): A61 K 9/127

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw De

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Terms	Documents
L1 and (ph adj gradient)	24

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